Idiopathic Anaphylaxis

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Course # 1605

Objectives

- Review definition and classification of idiopathic anaphylaxis
- Consider the differential diagnosis
- Critique lab tests/procedures used in the work up of patients with idiopathic anaphylaxis
- Examine treatment recommendations

Definition of Idiopathic Anaphylaxis

- "…is anaphylaxis not explained by a proved or presumptive cause or stimulus. It becomes a diagnosis of exclusion after other causes have been considered, such as *foods, medications, exercise, food and exercise, insect stings or bites, mastocytosis, and C1 esterase inhibitor deficiency/dysfunction*."
- Greenberger PA. Idiopathic anaphylaxis in Immunol Allergy Clin NA 2007;27:273-93.

Besides The Careful History, The Work Up

- May include skin and *in vitro* tests for serum specific IgE to foods and drugs, serum IgE to galactose-alpha-1,3-galactose (alpha-gal), baseline and acute phase serum tryptase, 24-hour urinary histamine metabolites, urinary prostaglandin D_2, oral challenges, peripheral blood for the mutation of the gene D816V and in some cases, a bone marrow examination.

Idiopathic Anaphylaxis

Mast cell activation but a diagnosis of exclusion

Tryptase elevated acutely

Urine Histamine elevated acutely (even with tongue or uvula enlargement) IA-Angioedema

B cell activation CD19+CD23+

Responsiveness to prednisone/H1 antagonists

Normal C4 and complements

+ Prick skin tests to foods non-contributory

Conditions/Initials

- Indolent Systemic Mastocytosis (ISM)
- Monoclonal mast cell activation syndrome (MMAS)
- Mast cell activation syndrome (MCAS)
- Idiopathic anaphylaxis (IA)

Classification of Idiopathic Anaphylaxis

- IA-*Generalized* (urticaria, angioedema, respiratory distress, upper airway angioedema, hypotension, abdominal pain, diarrhea)
- IA-*Angioedema* (urticaria, upper airway angioedema-obstructive)
- IA-*Questionable* (Urticaria without objective evidence of upper/lower airway obstruction, hypotension when syncopal etc)

Atopy in 48% of 333 IA Patients
Ann Allergy Asthma Immunol 1996;77:285-91

- Allergic rhinitis alone 19%
- Asthma alone 13%
- Allergic rhinitis and asthma 11%
- Food induced anaphylaxis 5%
- Atopic dermatitis 1.5%
- Pre-existing urticaria or angioedema 23%

Is There an Effect of Atopy on Anaphylaxis?

Yes

- Foods
- Latex
- Radiocontrast material
- Asthma
- Idiopathic anaphylaxis
- Exercise induced anaphylaxis
- Aspirin Exacerbated Respiratory Disease

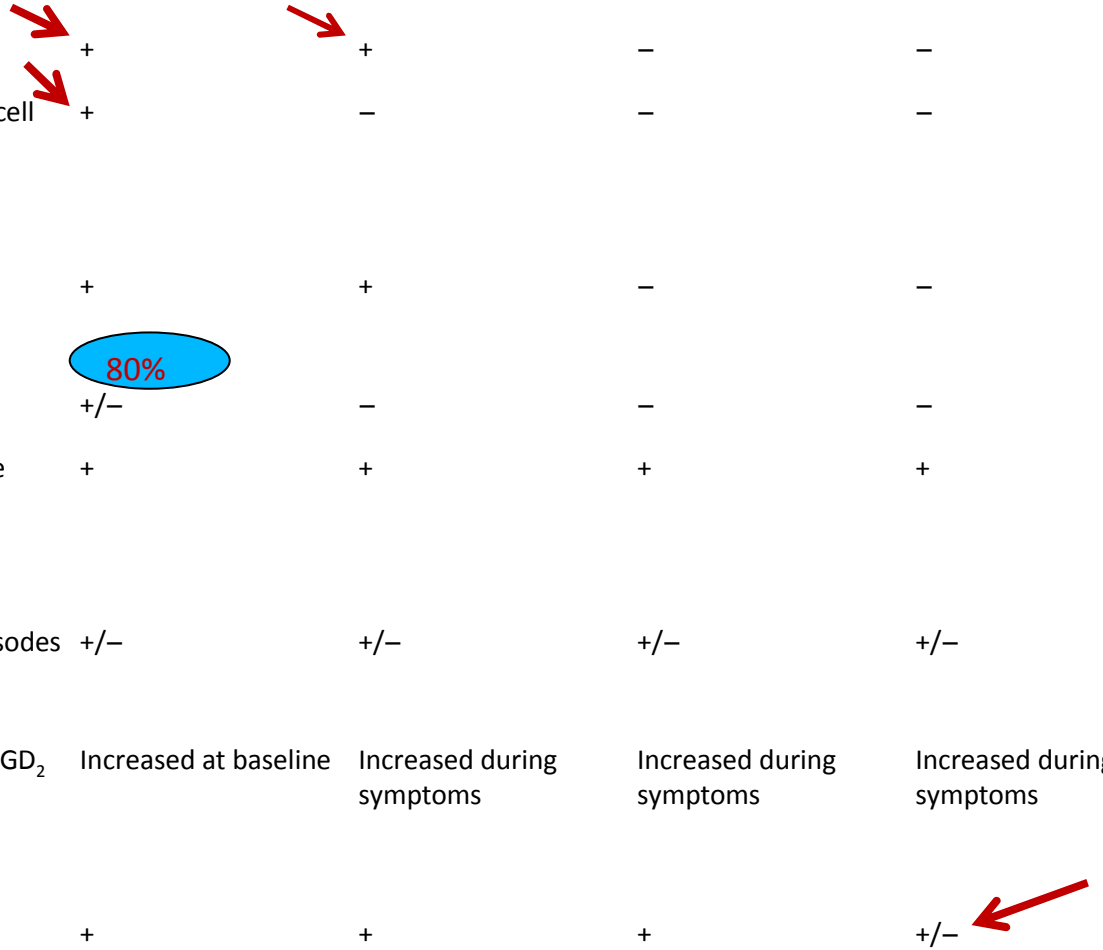
No

- Penicillin
- Muscle relaxants
- Hymenoptera stings
- Insulin

Idiopathic Anaphylaxis

- Considering and excluding other causes of anaphylaxis
- Being aware of new observations
- Knowing the patient and disease

	SM	MMAS	MCAS	IA*
Baseline tryptase	>20	Normal or mildly increased	Normal or mildly increased	Normal
c-kit D816V	+	+	–	–
Multifocal mast cell aggregates	+	–	–	–
Aberrant CD25	+	+	–	–
UP	+/–	–	–	–
Mediator release symptoms	+	+	+	+
Hypotensive episodes	+/–	+/–	+/–	+/–
Urine N-MH or PGD_2	Increased at baseline	Increased during symptoms	Increased during symptoms	Increased during symptoms
Response to antimediator therapy	+	+	+	+/–



Mast Cell Activation Syndrome
JACI 2010;126;1099-1104

1. Episodic symptoms (≥ 2) of Skin, GI, Cardiovascular, Wheezing, Naso-ocular
2. Decrease/resolution with anti-mediator therapy (H1, H2, LTRA or biosynthesis inhibitor or oral cromolyn)
3. Evidence of an increase in urinary or serum marker on ≥2 occasions when symptomatic
4. r/o primary or secondary causes of mast cell activation and idiopathic entities

Mast Cell Activation Syndrome
JACI 2010;126;1099-1104

- If baseline serum tryptase is > 15 ng/mL, require an *increase during symptoms* above baseline

Classification of Idiopathic Anaphylaxis……..

Terminology	Objective Evidence for Anaphylaxis ?
Idiopathic Anaphylaxis – Generalized	yes
Idiopathic Anaphylaxis – Angioedema	yes
Corticosteroid Dependent Idiopathic Anaphylaxis	yes
Malignant Idiopathic Anaphylaxis	yes
Undifferentiated Somatoform Idiopathic Anaphylaxis	no

Idiopathic Anaphylaxis- Tips

Atopy often present

May co-exist with Exercise Induced Anaphylaxis, chronic idiopathic urticaria and/or food allergy (anaphylaxis)

May be followed by PANIC ATTACKS not additional episodes of anaphylaxis

Rarely proved to be Indolent Systemic Mastocytosis, Mast Cell Activation Syndrome, Urticaria Pigmentosa….

Anaphylaxis Implies a Risk of Death……..

- Self injectable epinephrine (verify presence and use of demo)
- H1 receptor antagonist
- Oral albuterol (if tolerated)
- Prednisone for initial therapy

Pharmacologic Approaches to Idiopathic Anaphylaxis

Initial Therapy

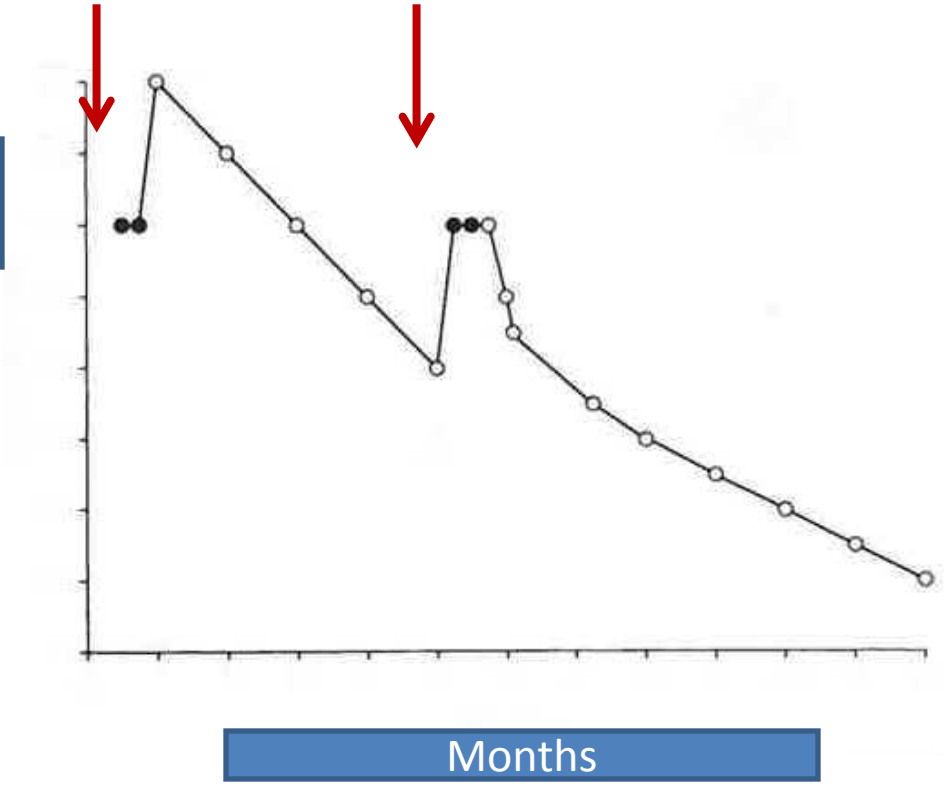
- Epinephrine auto-injector
- Cetirizine (or H1 receptor antagonist)
- Albuterol orally (if tolerated)
- Prednisone if severe or frequent

If not controlled, not more than cases described

- LTRA
- Oral cromolyn
- Oral ketotifen
- Azathioprine or tacrolimus (oral)
- Omalizumab (in literature)

Initial Treatment with Prednisone, H1 antagonist, Epi available

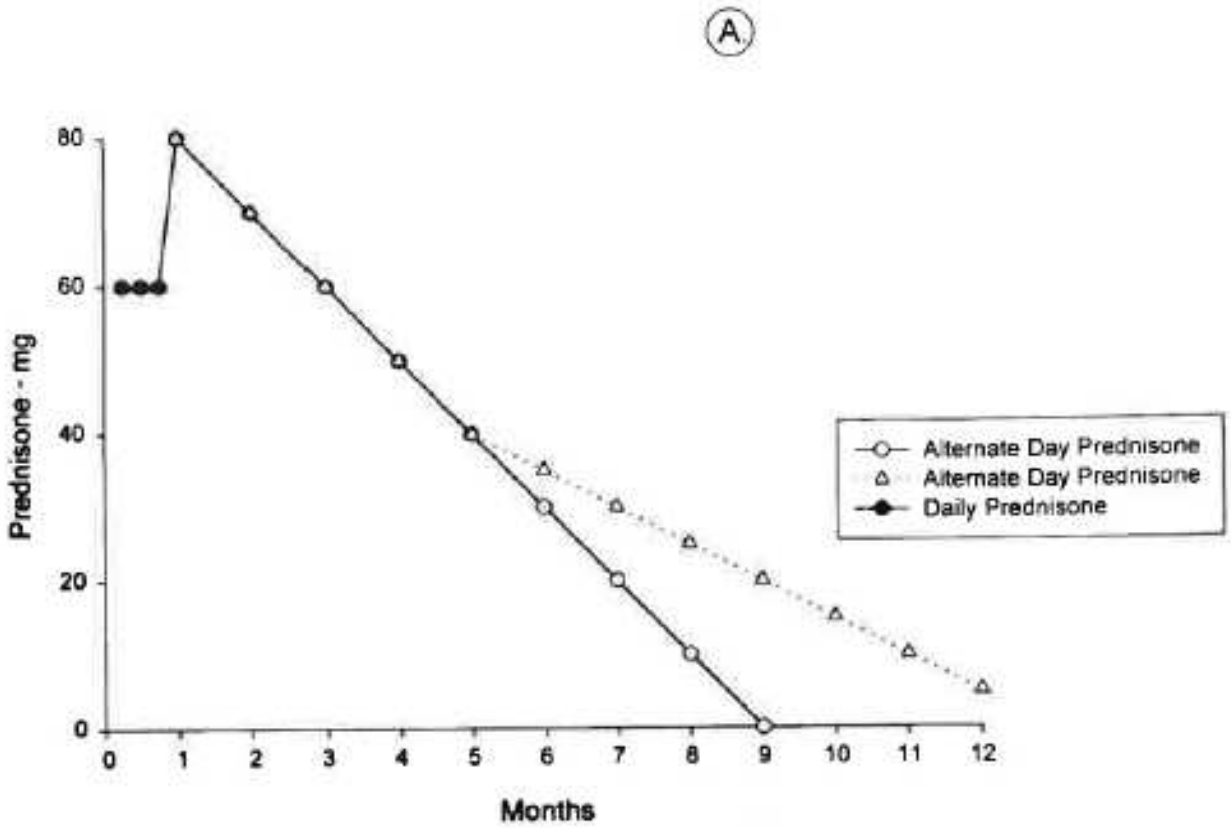
Prednisone 60mg



Months

- Prednisone alternate mornings
- Prednisone daily

Control of Episodes; Gradual tapering of Prednisone



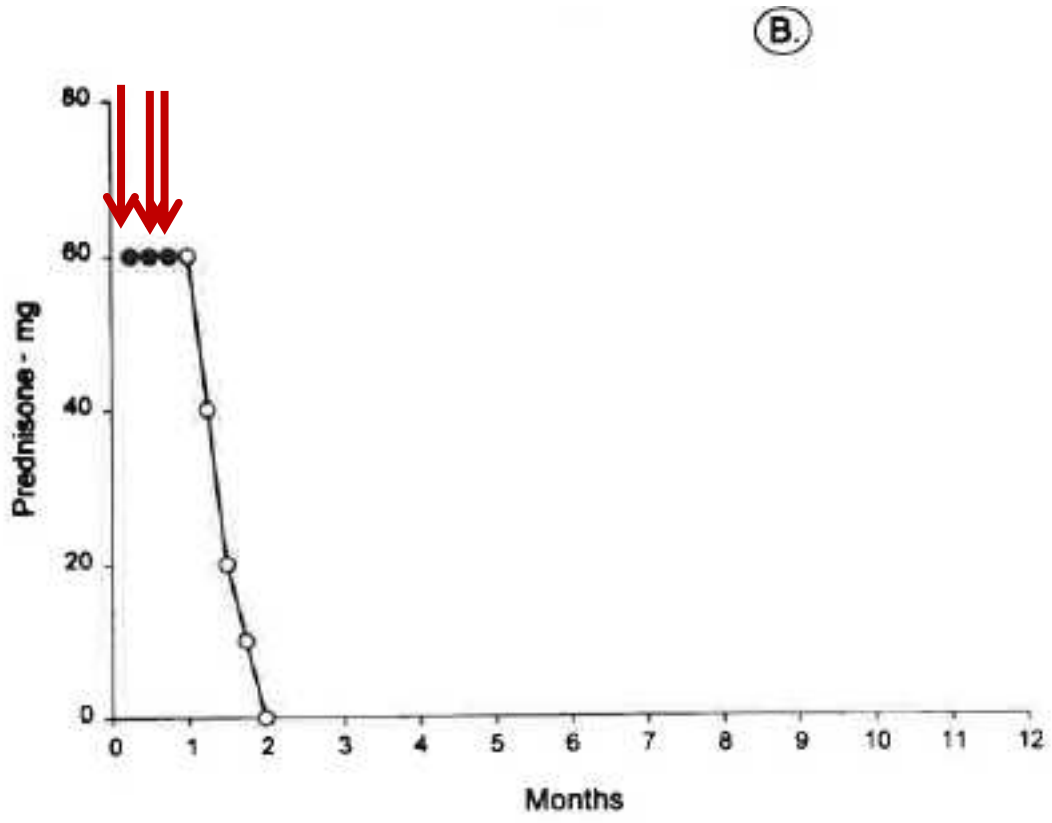
Practice Parameters on Anaphylaxis JACI 2010;126:477-80

- “Empiric use of oral steroids/H1 blockers has been demonstrated to reduce the frequency/severity of episodes (C)

Frequency of Idiopathic Anaphylaxis

- Frequent: 2 attacks in 2 months or 6 in 1 year
- Infrequent: < 6 attacks in 1 year

Ineffectiveness of Prednisone: Episodes Continue in First Month… Consider Undifferentiated Somatoform IA



Undifferentiated Somatoform-Idiopathic Anaphylaxis

US-IA…….JACI 1995;96:893-900

When prednisone increases attacks

When objective evidence cannot be confirmed

When there is no response to therapy

When the pt meets criteria for a somatoform disorder

Manage with non-steroid therapy

Pt typically won't obtain psychiatry consultation

Somatoform Condition

One or more physical complaints

Symptoms/signs lasting 6 months

and 1 or 2

1. Exam doesn't confirm objective evidence
2. Symptoms, impairment or physical problems are grossly out of proportion to physical exam findings

Urticaria (limited) + passing out (NL BP, pulse)

Idiopathic Anaphylaxis

- Considering and excluding other causes of anaphylaxis
- Being aware of new observations
- Knowing the patient and disease

Considering and Excluding Other Causes of Anaphylaxis …..Northwestern Experience

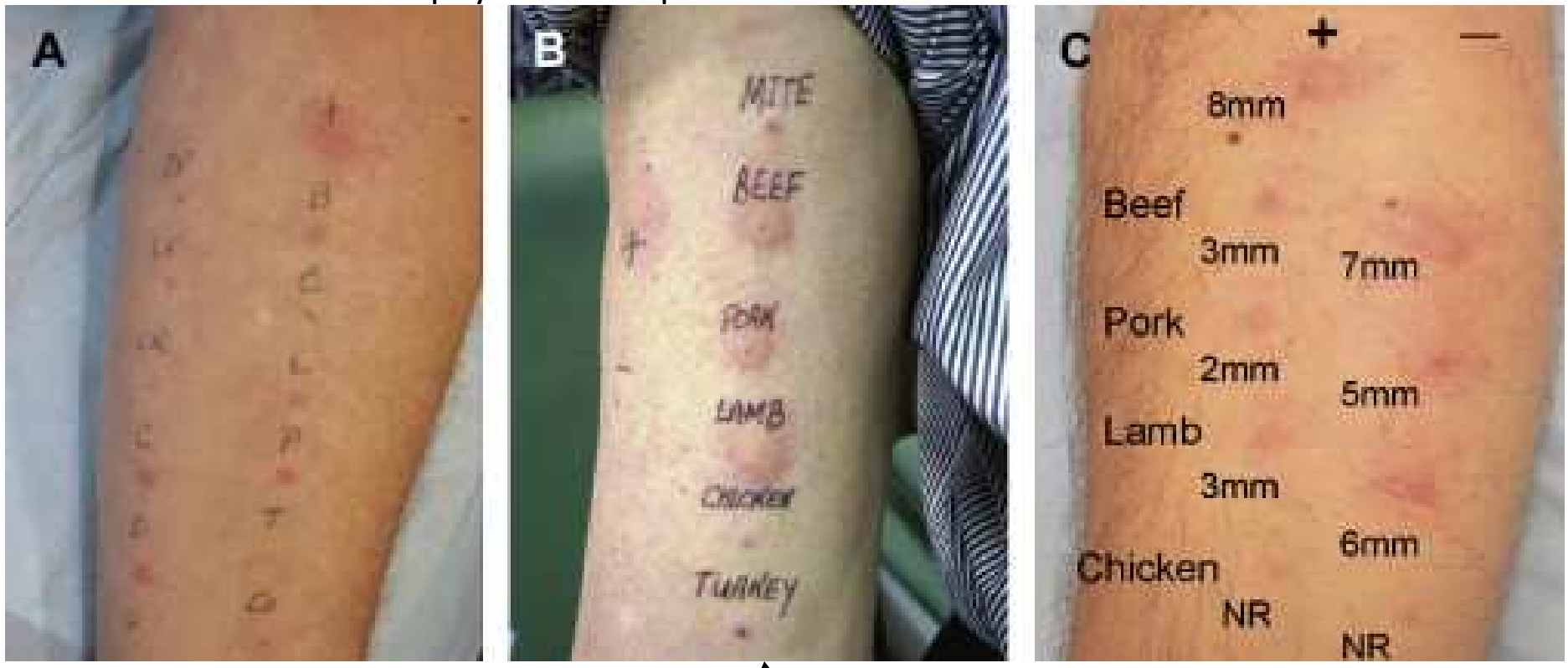
- "Hidden" Foods……..is allergic reaction > 3 hrs from onset…….or is it from beef, pork or lamb?
- Non-reported medication
- Bee pollen (pollens + molds) consumed
- $K_2S_2O_5$ (1mg, placebo, 5, 10, 25, 50, 100, 200= 391mg or 4x a heavily sulfited restaurant meal)
- MSG (81mg total challenge)
- Aspartame
- Papain (consumed)

Anaphylaxis Questions/Considerations re the oligosaccharide galactose-α-1,3-galactose?

- Questions: Has glycosylation of the Fab or Fc fragment made an immunoglobulin (cetuximab) immunogenic or *did a tick bite sensitize the patient to a SUGAR that caused anaphylaxis*?
- Does the patient report delayed (3-6 hours) onset urticaria (anaphylaxis) after *BEEF, PORK or LAMB*?
- Can the patient tolerate chicken, turkey and fish?
- Have there been tick bites?

Skin Tests to Foods prick, ID in Patients + for anti-alpha Gal IgE
JACI 2009;123:426-433

Time to Onset of Anaphylaxis in 10 patients: “1-2” to 6 hours



Intradermal Food Tests

The % of Anti-Alpha Gal IgE in the U. VA. Allergy-Immunology Pediatric Service

- 24% of 142 children/adolescents ages 4-18 seen for wheezing
- Pediatrics 2013;131:e1345-e1552
- Presumably sensitized by tick bites

How Would You Describe the Urticarial Lesions that Accompany

- Carcinoid Syndrome
- Pheocromocytoma
- Scromboid poisoning
- Non-Scromboid poisoning